P2-033 BSTB: Cancer Genetics Posters, Tue, Sept 4

Polymorphisms of Jak3 contribute to diminished promoter activity and increased risk of lung cancer in Korea populations

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In process lung SNP(single nucleotide polymorphism) targeting studies, we knew that JAK-STAT signaling pathway is responsible for several apoptotic and cell cycle regulatory proteins. The family of Jak kinases is composed from at least four non-receptor kinases(Tyk2, Jak1, Jak2, Jak3). In generally, Jak3 is related lymphoid development, immune function and innate genetic disease. But, Jak3 is not well defined SNP studies of promoter region in lung cancer.

Therefore, we investigated whether SNPs of Jak3 promoter are associated with Korean lung cancer patients. We analyzed 5 SNP points(-1514, -866, -672, 64 and 227) of Jak3 promoter by using the genomic DNA from 320 Korea lung cancer patients and 268 healthy controls. Genotyping was performed by the SNP-IT, SNapShot assay and Restriction Fragment Length Polymorphism (RFLP). The allele frequencies of each SNP between lung cancer patients and controls were estimated by the chi-square tests and odds rations (OR) with 95% confidence interval (95% CI). We explored the association between SNP points and histopathological factors of the lung cancer patients. Also, using these 5 SNPs, linkage disequilibrium and haplotype patterns were examined.

To these 5 SNP points, -672 point was associated with lung cancer risks. In case of -672 SNP point, subgroup analysis of clinicopathologic parameters in cancer group showed significant differences in male, non-smoker and non-drinker. In vitro assay, transfection of A549, H1666, Calu1 and H1299 NSCLC cell lines with luciferase reporter constructs containing 769 bp of the -672 point(-672 G/A) showed difference luciferase activity expression patterns.

In conclusion, we confirmed a relation between the Jak3 gene polymorphisms and significant increased risk in certain subgroup of lung cancer patients. SNPs of Korean lung cancer patient in Jak3 promoter are related to clinicopathologic parameters in male, non-smoker and non-drinker.

In this study, we investigated to single nucleotide polymorphisms (SNPs) in the JAK3 and the relationships between the SNPs and the risk of lung cancer occurrence in Korean lung cancer patients compared to normal controls. This is the first study to provide evidence for an association of JAK3 gene polymorphisms with lung cancer risk.

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The molecular mechanism of Nm23-H1 gene transfection on reversing invasion and metastasis phenotype in human high-metastatic large cell lung cancer cell line L9981

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Background: Our previous studies have proved that nm23-H1 gene was a tumor metastatic suppressive gene, tumor metastasis phenotype of human lung cancer could be reversed by transfection of nm23-H1 cDNA, but the molecular mechanism of nm23-H1 for inhibiting tumor invasion and metastasis is unclear. The aim of this study is to explore the molecular mechanism of nm23-H1 reversing the invasion and metastasis phenotype in human high-metastatic large cell lung cancer line L9981.

Methods: The cell growth and the invasive ability were detected in L9981 (the primary lung cancer cell line), L9981-pLXSN (the lung cancer cell line transfected with vector) and L9981-nm23-H1 (the lung cancer cell line transfected with nm23-H1) by MTT assay and modified Boyden chamber, respectively. The mRNA and protein expression of β-Ccatenin, E-Cadherin, CD44S, CD44V6, MMP-2, TIMP-1, VEGF were detected in the same three lung cancer cell lines by RT-PCR and Western blot. The change of gene expression and signal transduction were determined before and after transfection of nm23-H1 gene by microassay.

Results: Cell proliferation, clone formation and invasive ability in the L9981-nm23-H1 lung cancer cell line transfected with nm23-H1 gene were significantly lower than those in L9981 and L9981-pLXSN lung cancer cell lines($P<0.001$).No Significant difference of cell proliferation, clone formation and invasive ability was observed between in L9981 and L9981- pLXSN lung cancer cell line($P<0.05$). The mRNA and protein expression of β-Ccatenin, E-Cadherin, TIMP-1 were significantly up-regulated in L9981- nm23-H1 lung cancer cell line transfected with nm23-H1 cDNA than those in L9981 and L9981-pLXSN lung cancer cell lines ($P<0.001$), but no significant difference of mRNA and protein expression of β-Catenin, E-Cadherin and TIMP-1 existed between L9981 and L9981-pLXSN lung cancer cell line($P<0.05$). The mRNA and protein expression of MMP-2, CD446V and VEGF were significantly down-regulated in the L9981-nm23-H1 lung cancer cell line than those in L9981 and L9981-pLXSN lung cancer cell lines ($P<0.001$), but no significant difference of mRNA and protein expression of MMP-2, CD446V and VEGF existed between L9981 and L9981-pLXSN lung cancer cell line($P>0.05$). 24 gene related to metastasis were upregulated and 34 gene related to metastasis were down-regulated after transfection of nm23-H1 gene. 36 genes related to signal pathway were up-regulated and 29 genes related to signal pathway were down-regulated after transfection of nm23-H1 gene.

Conclusions: (1) nm23-H1 might be a key regulatory gene of metastsis related genes and it may play an important role in the Lung Cancer Metastatic Suppressive Cascde. (2) nm23-H1 gene can reverse the invasive and metastasis phenotype of human high-metastatic large cell pulmonary carcinoma cell line L9981 through regulation of the expression of metastatic genes and signal transduction pathway.

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